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(54) **REVETEMENT DESTINE A UNE MATIERE BIOLOGIQUE POUVANT ETRE INTRODUITE DANS LE FLUX SANGUIN OU DANS LE TISSU DU CORPS HUMAIN**

(54) **COATING FOR BIOMATERIAL WHICH CAN BE INTRODUCED INTO THE BLOODSTREAM OR INTO THE TISSUE OF THE HUMAN BODY**

(57) L'invention concerne un revêtement contenant une composition dont les constituants sont solubles dans un solvant, de préférence dans le chloroforme. Cette composition comprend un excipient de médicament, par exemple poly-D, L-lactide, des inhibiteurs de la sérine protéase, de préférence des inhibiteurs de la thrombine, ainsi que de la prostaglandine ou de la prostacycline ou leurs dérivés. Ce revêtement permet à la matière biologique revêtue de se décomposer lentement dans le tissu ou le flux sanguin et d'empêcher la formation de thromboses.

(57) The coating consists of a composition, the components of which are soluble in a solvent, preferably chloroform. In detail, they are a medicament carrier like poly-D, L-lactide, serine protease inhibitors, advantageously thrombin inhibitors and prostaglandines or prostacyclines or derivatives thereof. With such a coating, coated bio-material in the tissue or in the bloodstream are continuously slowly decomposed and the formation of thromboses is prevented.

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Mit internationalem Recherchenbericht.
Vor Ablauf der für Änderungen der Ansprüche zugelassenen Frist. Veröffentlichung wird wiederholt falls Änderungen eintreffen.

(54) Title: COATING FOR BIO-MATERIAL INSERTABLE INTO THE BLOODSTREAM OR TISSUE OF THE HUMAN BODY

(54) Bezeichnung: BESCHICHTUNG FÜR IN DEN BLUTSTROM ODER IN DAS GEWEBE DES MENSCHLICHEN KÖRPERS EINBRINGBARES BIOMATERIAL

(57) Abstract

The coating consists of a composition, the components of which are soluble in a solvent, preferably chloroform. In detail, they are a medicament carrier like poly-D, L-lactide, serine protease inhibitors, advantageously thrombin inhibitors and prostaglandines or prostacyclines or derivatives thereof. With such a coating, coated bio-material in the tissue or in the bloodstream are continuously slowly decomposed and the formation of thromboses is prevented.

(57) Zusammenfassung

Die Beschichtung besteht aus einer Zusammensetzung, deren Komponenten in einem Lösungsmittel, vorzugsweise Chloroform, löslich sind. Im einzelnen sind diese ein Arzneistoffträger, wie Poly-D, L-Laktid, Inhibitoren gegen Serinproteasen, vorzugsweise Thrombininhibitoren und Prostaglandine bzw. Prostazykline oder Derivate hiervon. Mit einer derartigen Beschichtung wird überzogenes Biomaterial im Gewebe bzw. im Blutstrom kontinuierlich langsam abgebaut und die Bildung von Thrombosen verhindert.

Coating for biomaterial which can be introduced into the bloodstream or into the tissue of the human body

The invention relates to a coating for biomaterial which can be introduced into the bloodstream or into the tissue of the human body. This term is used to designate, for example, infusion catheters, cardiac catheters, balloon catheters, electrodes, suture materials for vessel anastomoses, oxygenators, vessel prostheses or supports for vessels, called stents, etc., which remain for a short time or else for a long time directly in arteries and veins and in body tissue or come into contact with blood. The hazards for the patients, for example due to thrombosis formation and inflammations, are known and have to be considered with regard to the success of therapy and severity of the disorder.

EP-A1-0578998 discloses the production of such biomaterial with a covering of a biodegradable material, for example poly-D,L-lactide, with medicaments then also being incorporated into this biodegradable material and, on degradation of the biomaterial in the implanted state, being gradually released at, preferably, a constant rate to the patient. Heparin is mentioned, for example, as medicament which, incorporated in dispersed form, then specifically reaches the blood circulation and speeds up the action of plasmatic inhibitors such as antithrombin III and heparin cofactor II as catalyst thereof.

It has furthermore been proposed, in German Patent Applications P 43 34 272.8 and P 44 35 652.8, to coat biomaterial with a biodegradable material, with the coating being very thin with layer thicknesses of less than 100 micrometers so that only the primary structure of the biomaterial is covered. If, for example, the

primary structure is a network structure as is the case with said vessel prostheses or stents, only the individual strands of the prosthesis are coated; in no case is the prosthesis enveloped by a complete casing. It has emerged with a paint-like coating of this type that an antithrombogenic effect is achieved merely by the slow biological microdegradation of the coating material. The coating material used in this case comprises biodegradable synthetic polymers such as polyglycols and polylactides, and corresponding copolymers or mixtures etc., which are dissolved in an organic solvent, preferably chloroform, which evaporates after application to the biomaterial.

It is also proposed in these patent applications to incorporate medicinal substances into the coating material, using as medicinal substances both anticoagulant and antiinflammatory medicinal substances. The incorporation of antibiotics is also possible. However, in contrast to the abovementioned process, these medicinal substances are intended not to be released to a large extent into the bloodstream but to act essentially locally.

It has emerged from experiments that the formation of thrombi can be prevented to a large extent with a paint-like coating of this type, where appropriate in combination with incorporated medicinal substances, so that the surgical risks which are always a worry otherwise can be greatly reduced.

The invention is based on the object of indicating a coating material in which the advantageous effects can be further increased.

This object is achieved according to the invention by the features of claim 1.

According to this, at least one inhibitor of serine proteases which, just like the medicinal substance carrier itself, is it itself able to dissolve in the organic solvent necessary for preparation of the coating material, preferably chloroform, is used. This results in a homogeneous solution, which is applied to the biomaterial, after which the solvent is subsequently evaporated off so that a dissolved homogeneous mixture is then present as coating on the biomaterial. The inhibitor is a directly acting thrombin inhibitor, i.e. acts without the involvement of an endogenous cofactor or the like.

Another homogeneously dissolved medicament which can also be present is a prostaglandin or prostacycline, it additionally being possible to incorporate fast-acting antithrombogenic agents such as hirudin.

The medicinal substance carrier preferably used is a poly-D,L-lactide which can be bought as R203 from Boehringer, Ingelheim; the antithrombin preferably used is an amidinophenylalanine derivative as claimed in claims 9 and 10, which is marketed by Behring-Werken AG under the name CRC220 and is described in detail in EP-A1-0513543.

The provision of a coating material according to the present invention was based on the idea that endothelial cells have, as inner linings of blood vessels, mechanisms which prevent adhesion of cells and plasma proteins. In this connection, released substances such as prostaglandins in particular prevent the deposition of blood platelets; in addition, substances which counteract thrombin formation are produced on the surface.

It has now emerged from the experiments for the present invention that so-called self-cleaning surfaces, i.e. permanently biodegradable materials, in combination

with homogeneously dispersed inhibitors of thrombin and serine proteases, and, where appropriate, prostaglandins or prostacycline derivatives or appropriate analogs, which are incorporated in dissolved form into the coating materials, have an endothelium-like action. The result of this is, while there is only low systemic availability of the incorporated dissolved medicaments, by combination with the self-cleaning surface coating there is prevention of deposition, of activation of plasma coagulation and of blood platelet aggregation. The coating material can be referred to, as it were, as long-term depot, the aim being to keep the release of the medicaments, in particular of the antithrombins, as low as possible in order not to result in the known disadvantages of systemic dosage.

A so-called triple combination consisting of thrombin inhibitors such as hirudin and said CRC220 with a synthetic prostaglandin derivative (iloprost) has proven useful on introduction into the blood circulation of implants or prostheses which are associated with a particularly high risk of activating coagulation. In this case, the hirudin acts as thrombin inhibitor which is rapidly available directly in the surgical phase and by which the complication of the surgical intervention is reduced. The inhibitors which are also homogeneously dispersed in the medicinal substance carrier then bring about the necessary long-term compatibility.

The coating material according to the invention is produced by initially preparing a basic solution of a medicinal substance carrier, preferably poly-D,L-lactide, and a solvent, preferably chloroform. For the solution, 50 to 300 milligrams, preferably 150 to 160 milligrams, of a medicinal substance carrier are dissolved in one milliliter of solvent, preferably chloroform.

Said antithrombin CRC220 is dissolved in this basic solution to result in a content of between 0.5 and about 20% by weight, preferably up to 10% by weight, in the final mixture based on the medicinal substance carrier. Furthermore, said prostaglandin derivative Iloprost is also dissolved in a content between 0.5 and 7% by weight, preferably 1 to 5% by weight, and finally hirudin is added in a content between 2 and 10% by weight of the complete solution, preferably about 5% by weight.

After application of this solution to biomaterial, the chloroform evaporates so that a homogeneous mixture of medicinal substance carrier and added medicaments is then present as coating.

Claims

1. A coating for biomaterial which can be introduced into the bloodstream or into the tissue of the human body, such as infusion, cardiac or balloon catheters, electrodes for heart pacemakers and defibrillators, suture material, oxygenators, support constructions for vessels (stents) or the like, this coating preventing in particular blood coagulating on the biomaterial due to adhesion of plasmatic or cellular constituents, and the coating having a blood- and tissue-compatible medicinal substance carrier which is dissolved in an organic solvent, and in which at least one medicament is incorporated and which, after application to the biomaterial and evaporation of the solvent, is permanently biodegraded in the body, wherein an inhibitor of serine proteases is present in homogeneously dispersed dissolved form in the medicinal substance carrier, this inhibitor being soluble together with the medicinal substance carrier in the same organic solvent, so that application to the biomaterial and evaporation of the solvent result in a homogeneous coating which is composed of medicinal substance carrier and inhibitor and has a function comparable to that of endothelium.

2. A coating as claimed in claim 1, wherein the inhibitor is a directly acting thrombin inhibitor.

3. A coating as claimed in claim 2, wherein the thrombin inhibitor suppresses contact activation of blood coagulation.

4. A coating as claimed in any of the preceding claims, wherein, to achieve an endothelium-like

action, furthermore a prostaglandin or prostacycline or a corresponding derivative is added together with the medicinal substance carrier and the inhibitor to the solvent and is contained in dissolved form in the medicinal substance carrier.

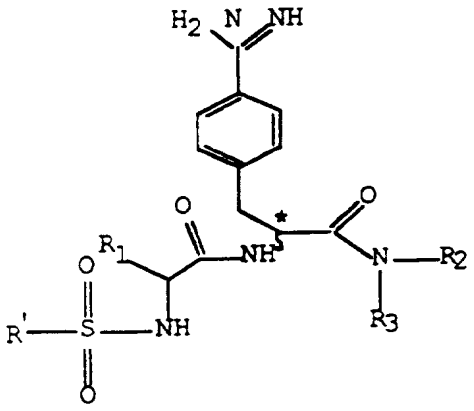
5. A coating as claimed in any of the preceding claims, wherein additionally an antithrombin which can be rapidly released, such as hirudin, is incorporated into the medicinal substance carrier.

6. A coating as claimed in any of the preceding claims, wherein a poly-D,L-lactide is used as medicinal substance carrier.

7. A coating as claimed in any of the preceding claims, wherein the individual components of the coating are dissolved in chloroform.

8. A coating as claimed in any of the preceding claims, wherein the coating forms on the biomaterial a paint-like adhesive layer with layer thicknesses of less than 100 micrometers, preferably less than 50 micrometers or 10 micrometers.

9. A coating as claimed in any of the preceding claims, wherein a compound of the following structure is used as soluble antithrombin:



in which R′ is a naphthalene ring which is bonded in the alpha or beta position and is optionally derivatized with alkyl groups which contain up to 3 carbon atoms, and/or alkoxy groups with in each case up to 3 carbon atoms, or is a tetralin ring or indane ring which is bonded in the alpha or beta position and which is optionally derivatized with alkyl groups which comprise up to 3 carbon atoms, and/or else alkoxy groups with in each case up to 3 carbon atoms, or is a phenyl ring which is optionally derivatized with alkyl groups which contain up to 4 carbon atoms, and/or with up to three groups of the structure O-X in which O is oxygen and X is hydrogen, methyl, ethyl, n-propyl, i-propyl or tert-butyl, and/or with a group of the structure -COOY in which Y is hydrogen, methyl, ethyl, n-propyl, i-propyl, tert-butyl, i-butyl, i-pentyl or neo-pentyl, or is a chroman system which is preferably derivatized with up to 5 alkyl groups which contain up to 3 carbon atoms, is a group of the structure A-B where A = $-(CH_2)_n-$ and n = 1-4 and B is an acid functionality selected from the group consisting of carboxyl functionality which can optionally be esterified or be in an amide form, where the esters contain an alcohol with up to 17 carbon atoms, sulfonic acid functionality, a functionality of a phosphorus

acid, a boronic acid functionality and tetrazole group, or R_1 is a group of the structure A-B-C where A has the above meaning, B is carbonyl or sulfonyl, and the group C is derived from an N-bonded alpha, beta, gamma or delta amino acid or from the group of N-glycosidically linked uronic acids, and R_2 and R_3 can be identical or different and are alkyl groups with up to 4 carbon atoms or together form a heterocyclic ring which has up to 8 ring members and can be derivatized with a hydroxyl group or a hydroxyalkyl group with up to 3 carbon atoms, and this hydroxyl group is optionally in esterified form, where the corresponding acids are carboxylic acids which contain up to 17 carbon atoms, and in which the carbon atom labeled with * has the R or S structure, but preferably the R structure (CRC220).

10. A coating as claimed in claim 9, wherein R' is 4-methoxy-2,3,6-trimethylphenyl, R_1 is $-CH_2-COOX$ with X equal to hydrogen and R_2 and R_3 together are piperidine.

11. A coating as claimed in any of the preceding claims, wherein the components of the coating are present dissolved in a solvent, preferably chloroform, where the contents of the individual components per milliliter of the solvent have the following values:

100 to 300, preferably 150 to 160, milligrams of medicinal substance carrier;

0.5 to 20% by weight, preferably up to 10% by weight, of a directly acting antithrombin (CRC220);

0.3 to 2% by weight, preferably 0.5-1% by weight, of a prostaglandin derivative or of a corresponding analog;

0.5 to 10% hirudin.

12. A coating as claimed in claim 10, wherein the mixture preferably comprises 5% by weight of each individual substance.